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STUDY TO KNOW THE SIMVASTATIN EFFECTS ON INSULIN SENSITIVITY IN TYPE II DABETIC PATIENTS

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Abstract:

Objective: *To investigate the effect of simvastatin treatment on insulin sensitivity in type 2 diabetes mellitus patients.*

Study Design: *A randomized case control study.*

Place and duration: *In the Medicine Unit II of Holy Family Hospital Rawalpindi for one year duration from January 2018 to January 2019.*

Methods: *The study was performed on 100 subjects with type 2 diabetes in both genders. Into two groups, patients were randomized. 50 subjects received Simvastatin 40 mg / day for 3 months and 50 volunteers were taken as controls. Both groups had same anthropometric properties (duration of diabetes, age, blood pressure and BMI) and biochemical (fasting plasma glucose, serum creatinine, lipid profile and fasting insulin level). Simvastatin (40 mg / day) was evaluated by insulin resistance (HOMA-IR) for the evaluation of homeostasis model for resistance of insulin after and before 3 months of management.*

Results: *Simvastatin (40 mg / day) significantly reduced triglyceride, cholesterol and LDL levels but did not affect significantly sensitivity of insulin as determined by HOMA-IR. However, sensitivity of insulin was increased in people with resistance to insulin (P = 0.001 reduction, HOMA IR 1.92).*

Conclusion: *Although short-term treatment with simvastatin (3 months) had no effect on sensitivity of insulin, lipid depletion had strong effect on all cases.*

Key words: *Insulin sensitivity, Diabetes, Simvastatin, lipid profile.*

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INTRODUCTION:

According to the (IDF) International Diabetes Federation Diabetes Atlas, it is estimated that in 2003 worldwide 194 million people affected by diabetes mellitus and affected 299-333 million people in 2025. Pakistan will be the sixth with 6.2 million diabetic patients in the world and fourth with 11.7 million diabetic patients in 2003[1]. In the diabetes development an important role is of Insulin resistance. Although the level of diet, physical activity and genetics is supposed to play an important role, the exact form of resistance to insulin in type 2 diabetes is still not clear[2]. Several studies showing the effects of HMG-Co-A reductase inhibitors on sensitivity of insulin in type 2 diabetic patients reported that two different studies using simvastatin and atorvastatin increased the statins effect on insulin[3]. Although it has not observed an effect, it is important that statins are widely used in the hypercholesterolemia treatment clinically. Knowing the effect on insulin sensitivity and the cost-benefit analysis of these intercession would be more favorable than studies done previously[4]. Therefore, our goal was to investigate whether treatment with simvastatin (40 mg / day) for three months affected insulin sensitivity in patients of type 2 diabetes determined by Homeostasis Model Assessment (HOMA-IR).

MATERIALS AND METHODS:

This randomized case control study was held in the Medicine Unit II of Holy Family Hospital Rawalpindi for one year duration from January 2018 to January 2019. The study was approved by the corporate ethics review board. 100 total type 2 diabetic patients were taken from the OPD. The procedure and aim of the analysis are explained to every individual. In two groups; Patients were randomized, 40 mg daily simvastatin was given to 50 people for three months and as a control total 50 were taken. Subjects who already used antihypertensive or metformin drugs allow to continue their medicine, but throughout the study period modification of dose was going on. Inclusion criteria: Over 30 years of age, type 2 diabetes, blood pressure below 140/90 mmHg.

Exclusion criteria: history of liver, kidney or heart disease, kidney transplantation history, alcohol dependence or recent history of drug, pregnancy or labor, use of insulin, use of statins or steroids, serum creatinine above 1.5 mg / dl, LDL levels above 130 mg / dl and.

Data collection: weight, height, blood pressure and BMI measurements were made and other data were collected with the help of a questionnaire which was designed previously.

Biochemical parameters: fasting insulin, fasting blood glucose, triglycerides, LDL, HDL, fasting lipid profile (cholesterol, statistics were sent by using ELISA 303 standard methods. Serum creatine levels and ALT were also recorded before and after the analysis. Evaluation of insulin sensitivity: Evaluation of the homeostasis model (HOMA-IR) was assessed by evaluating insulin sensitivity as follows: insulin (mu / ml) glucose (mmol / l) /22.5. On insulin sensitivity; the effect of simvastatin did not increase or decrease HOMA-IR values after treatment for three months. With SPSS 18.0 Statistical analysis was done. Chi-square test (for categorical variables) and T test (for continuous variables) was used to compare the reference characteristics between the control groups and drugs given group. To estimate the statistical significance of the differences in the tools before and after the processing of continuous variable; paired T test was used.

RESULTS:

Table I shows the biochemical and anthropometric properties of the selectees in the treated group with simvastatin and control group at the beginning of the study.

Table-I: Anthropometric characteristics of Type 2 Diabetes Subjects in Control and Simvastatin group

Variable	*Control group (n=39)*	*Simvastatin group (n=42)*
†Gender		
Male	26(66.7%)	23(54.8%)
Female	13(33.3%)	19(45.2%)
†Family History		
No	14(35.9%)	17(40.5%)
Yes	25(64.1%)	25(59.5%)
†Systolic Blood Pressure		
<130 mmHge	15(42.9%)	16(40.0%)
≥130 mmHg	20(57.1%)	24(60.0%)
†Diastolic Blood Pressure		
<85 mmHge	26(74.3%)	24(60.0%)
≥85 mmHg	9(25.7%)	16(40.0%)
*Age (in years)	49.72 ± 8.51	49.93 ± 10.69
*Duration of diabetes (in years)	7.66 ± 4.91	6.13 ± 5.29
*BMI (Kg/m²)	27.97 ± 4.76	27.59 ± 4.33

† Numbers (percentages) reported for categorical variables.

In both groups; male to female ratio was same. The proportion of individuals with a family diabetes history and hypertension was similar in both groups.

Table-II: FPG, Insulin and Lipid Profile of Control group

Variable	*Control group*	
	Baseline	*After 3 months*
Fasting Plasma Glucose (mg/dl)	156.32 ± 46.64	162.82 ± 70.39
Insulin (µU/mL)	10.03 ± 5.68	8.23 ± 3.97
Total Lipids (mg/dl)	716.43 ± 76.59	711.83 ± 123.04
Cholesterol (mg/dl)	167.85 ± 17.58	166.52 ± 18.97
Triglycerides (mg/dl)	135.13 ± 33.26	148.85 ± 80.75
HDL (mg/dl)	41.37 ± 2.06	40.52 ± 2.48
LDL (mg/dl)	100.23 ± 15.99	95.6 ± 19.47

Both groups had same age, body mass index, similar serum creatinine levels and diabetes duration. The mean values of biochemical parameters are given in Table II at the beginning and end of the analysis in the control group (after three months). Table III shows the biochemical parameters value at the beginning and end of the study (treatment with simvastatin after 3 months).

Table-III: Changes in Biochemical parameters in Drug Group

Variable	*Drug Group*	
	Baseline	*After treatment*
Fasting Plasma Glucose (mg/dl)	153.55 ± 56.70	147.95 ± 34.49
Insulin (µU/mL)	9.59 ± 6.12	8.87 ± 4.64
Total Lipids (mg/dl)*	750.13 ± 148.54	682.42 ± 106.50
Cholesterol (mg/dl)*	171.9 ± 22.49	156.93 ± 14.03
Triglycerides (mg/dl)*	169.85 ± 103.21	134.59 ± 44.10
HDL (mg/dl)	40.39 ± 3.45	41.18 ± 2.47
LDL (mg/dl)*	100.55 ± 18.79	89.20 ±13.33
CPK (mg/dl)	113.53 ± 34.53	118.92 ± 17.89
ALT (mg/dl)	29.65 ± 31.19	22.0 ± 4.47

* p value < 0.05

Total lipid, cholesterol, triglycerides and LDL levels (40 mg / day), [40 mg / day] (p = 0.003, p value <0.001, p value = 0.013 and p = 0.003 respectively) before and after treatment with simvastatin. CPK and ALT values did not have a negative effect on liver or muscles when compared at the beginning and after treatment (p = 0.146, p value = 0.351). There was no static difference in HOMA-IR in the simvastatin treated group. In addition, we evaluated the simvastatin effect on sensitivity of insulin in patients with type II diabetes only by selecting patients with insulin-resistant type 2 diabetes. In type 2 diabetes mellitus for the insulin resistance diagnosis the reference cut-off value was reported by Matthews et al. Therefore, all subjects with HOMA-IR values greater than 2.8 were selected at the beginning of the study. In this group; 20 total cases were identified. At the beginning of the study, HOMA-IR was 3.74 with an average of 5.74 and 3 months with simvastatin treatment. A statistically significant decrease was observed in HOMA-IR 1.92 [p = 0.001].

DISCUSSION:

In type 2 diabetic patients on insulin sensitivity the positive effect of statins have been proven on clinical studies[5]. Stewart et al. Farrer M et al. Reported that statins had no reaction on sensitivity to insulin. Hyperinsulinemic euglycemic clamp technique is "gold standard" to determine peripheral sensitivity of insulin and has been used in many analysis[6-7]. Various analysis have used HOMA-IR, which is better in measuring sensitivity of insulin and with euglycemic glucose clamp technique is comparable. Farrer M, et al noted that simvastatin reduced the concentration of triglyceride in plasma, but there were no significant changes in insulin levels and fasting plasma glucose and HbA1c in type 2 diabetic patients very similar to our results[8-9]. We also did not find a significant change in insulin sensitivity, simvastatin 40 mg / day for three months, a significant change in lipid profile was observed[10]. Some studies on epidemiology have shown the association between dyslipidemia and insulin resistance. The study of CARDIA analyzed lipid and insulin levels in white and black adults[11-12]. There was a positive correlation between triglycerides and plasma insulin concentration between two racial groups[13]. In 1992, similar study was done by the French Telecom which compared the insulin resistance syndrome characteristics in the Caribbean and the Caucasus, and noted that the highest concentration of insulin was related with increased triglyceride levels in the Caribbean group[14-15]. In our study, treatment with simvastatin (40 mg / day) reduced effectively triglyceride, LDL and cholesterol levels for three months, but have no effect in a significant change in sensitivity of insulin. Subjects with Type 2 diabetes have greater than 2.8 of HOMA-IR and have insulin resistance as described. Matthews had noted 1.92 HOMA-IR had a statistically significant decrease in insulin resistance (p-value = 0.001). This shows that, although simvastatin did not affect all subjects with type 2 diabetes, insulin sensitivity was increased in a selected group of insulin resistant type 2 diabetes at the beginning of the study.

CONCLUSION:

In this study, it was suggested that short-term simvastatin treatment (3 months) had no effect on

sensitivity of insulin, but all patients had a significant effect of lipid reduction. Longer studies are needed in greater area to determine the statins effect on insulin sensitivity.

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